PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW/20668	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/05357	International filing date *(day/month/year)* 10.12.2003	Priority date *(day/month/year)* 19.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D333/20		
Applicant CIPLA LTD		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.05.2004	17.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Boletti-Cremers, K Telephone No. +49 89 2399-8541

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/05357

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12	as originally filed

Claims, Numbers

1-10, 11 (part), 20-22	as originally filed
11 (part), 12-19	filed with telefax on 25.02.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,19,20
	No:	Claims	18,21,22
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	18-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

   see separate sheet

POINT I.

The amendments on file are acceptable according to the requirements of Art.34(2)(b) , last sentence PCT on the basis of the support pointed out by the Applicant on 23.02.2005.

POINT IV.

Non unity.

The claimed matter involves the presence of 3 different inventions which are not linked to each other by the same inventive concept and necessitate the analysis of the documents (1)-(5), which are the relevant prior art under different aspects.

Those 3 inventions are:

1. The resolution method of rac.duloxetine to prepare (+) duloxetine or its salts involved in claims 1-7 according to a method which involves the preparation of a diastereoisomerical salt prepared by the reaction of rac (+) duloxetine and a chiral acid.

2. The stereospecific methods to prepare (+) duloxetine or its salts according to claims 7-17 and which involve **essentially** the use of certain bases in combination with a phase transfer catalyst contrary to the prior art (1)-(5).

3. The still novel salts of (+) duloxetine **as pharmacologically active compounds** and the pharmaceutical compositions encompassing them according to claims 18-22.
Because the salts are also meant to be potential intermediates for the syntheses summarized under invention 1. or 2. , they could be also associated to those invention.
As the Applicant paid 2 additional examination fees , present examination report will deal with the 3 inventions.

POINT V.

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) EP-A-0 457 559.
(2) WO-A-00/61540.
(3) US-A-5 362 886.
(4) EP-A-0 273 658.
(5) Tetrahedron Letters,vol. 31, no. 49,1990 , pages 7101-7104.
(6) WO-A-03/062219 (point VI).

1. Novelty.

1.1 Since none of the examples of (1) relates to the resolution of the rac. (+/-) duloxetine with a chiral acid or the recycling of the (-) duloxetine to the rac (+/-) to the purpose to provide the starting material necessary for the preparation of the (+) duloxetine compound , process claims 1-6 on file are novel with respect to the content of (1).
As a mere consequence , the invention 1, as defined above, is novel towards the content of (1).

1.2 Moreover , as stands , example 1 of (1) encompasses the reaction of a chiral intermediate salt of the type (I) , namely (-) N,N-dimethyl-3-(2-thienyl)-3-hydroxy-propanamine) with 1-halonaphthalene , which is a compound of type (II) in the presence of a base , but without the use of a phase transfer catalyst and the intermediate of type (III) is demethylated , so that present process claims 7-17 are novel with respect to the content of (1). As a mere consequence , the invention 2 , as defined above, is novel towards the content of (1).

1.3 As shown at the end of example 1 of (1) (see page 7 of (1)) , the (+) salts of duloxetine are known compounds , but prepared differently from the processes on file.
Indeed, if qualified as a chiral **(+)** , a compound must possess a positive optical rotation , so that the end product of example 1 of (1) , which possesses an $[\alpha]_D^{25}$ of +84 and which is the demethylation product of previous step C as disclosed on page 6-7 of (1) , must be the (+) oxalate salt of duloxetine. Moreover , the same conclusions must be drawn from the content of claim 6 of (1) , which discloses the maleate salt of duloxetine.

Both examples fall within the scope of present claim 18, 21 and 22 for the reasons that a different process to prepare them does not render those compounds novel "per se" and that the compounds disclosed in (1) are also substantially free of the not desired isomer of

duloxetine and that the mere fact that they should contain not more than 1% of (-) duloxetine- thus be purer than those encompassed by the processes of the prior art- is not a criteria admissible to acknowledge novelty.

As a mere consequence, the **invention 3** , as defined above, is still not novel towards the content of (1).

2. In view of the fact that (2) does not disclose any example of the synthesis of (+) duloxetine, the claimed matter of the 3 inventions , as defined above, can be regarded as novel with respect to the content of (2) , even if said document already discloses generically the possible synthesis of duloxetine (see page 6, lines 29-33) under conditions (see page 6 and 7 of (2)) that show the analogy between present invention as claimed under claims 1-6 and the content of (2).

3. The process disclosed in (3) refers to the preparation of (+)duloxetine and its salts (see scheme of columns 1-2 and focus on the product of step D ; refer also to the whole content of preparation 2 , column 5 of (3), in combination with example 1 of (3)) prepared slightly differently from the methods on file because the process of (3) does merely not involve the use of phase transfer catalyst.
Since example 3 of (3) provides evidence that a salt of (+)duloxetine is a known compound , 21, 22 lack novelty for the same reasons set out under present point 1.3 , for the content of (1).
As for (1), the argumentation presented by the Applicant with respect to the novelty of the claims concerned towards the content of (3) cannot be followed by the IPEA.
As for (1) , invention 3 is not novel whereas the 2 other inventions are novel with respect to the content of (3).

4. The same conclusions as for the preceding documents is drawn from the content of (4) and (5) (see (4) , examples 14, 38 of (4) in combination with the passage on page 6 , lines 20-25 ; see reaction scheme on page 7102 and especially the compounds 1,7,7a and their preparation as disclosed in (5)), in that the salts of (+) duloxetine and (+) duloxetine are known compounds prepared differently and that consequently, invention 1 and 2 are novel with respect to the contents of those documents , whereas invention 3 according to claims 21 and 22 cannot be regarded as novel with respect to the content of (4) and (5) for equivalent reasons as for (1).

4.1 For the content of (4) a separate comment should be made, namely that even if examples 14 and 38 do not mention the preparatory details , the salts mentioned at those examples have been identified and characterised , whereas the description mentions the possible (different) methodologies to prepare them at page 6, lines 20-25 and that, consequently , the Applicant's argumentation of 23.02.05 cannot be followed.

4.2 For the content of (5) , another separate comment should be made , namely that achiral salts (as reaction product of an achiral acid and (+) duloxetine) are made and described in (5) and that such a matter is still part of claims 21 and 22 on file , for the reasons that a new method to prepare a known compound does not render said compound or its use in the preparation of a pharmaceutical composition novel.

5. Although (6) as filed on 13.01.2003 and published on 31.07.2003 and claiming a priority right on 24.01.2002, is not prior art according to the Chap II PCT proceedings, its content will not affect the novelty of the 3 inventions defined above in the regional European proceedings to come, because (6) discloses the diastereoisomerisation of a key intermediate for the preparation of the (+) duloxetine , but not explicitly their further transformation into the desired end products.

2. Inventiveness.

Invention 1.

In view of the evidence together with the comparative argumentation provided by the Applicant on 23.02.05, the first invention defined above is considered as inventive in that the process enables a higher enantiomeric purity as the most relevant prior art (1).

Invention 2.

In view of the prior art (1)-(5) , invention 2. can be regarded as inventive in that none of those documents tends to suggest that the combined use of a base and a phase transfer catalyst could be useful for the purpose of the preparation of (+) or rac duloxetine or their precursors (as in present claim 7).

Invention 3 .

In view of the fact that all the documents quoted above relate to numerous pharmacologically active compounds which are also encompassed by the processes on file , but that they are prepared differently in those documents , any of the still novel pharmacologically active compounds of present claims 18-22 cannot be regarded as inventive and , provided novelty could be restored unambiguously in those claims, the Applicant is invited to show either by argumentation or technical evidence , that the still novel pharmacologically active compounds on file possess any advantage or surprising feature when they are compared with those of the prior art (1)-(5) in order to enable the acknowledgment of the inventiveness of the application with respect to their contents.

The argumentation presented by the Applicant in this respect , cannot be followed for the reasons that his argumentation is merely based upon the quantitative aspect of preparation of the compounds involved in invention 3. and that , since said invention relates to compounds "per se" , compounds which appear from numerous documents to be known compounds (the chiral and non chiral salts of (+) duloxetine-see the novelty objections above) with a known pharmacological behaviour, the original objection as repeated above remains and is maintained.

Formal Point.

The Applicant will be invited , in the regional proceedings to come, to quote and briefly discuss one or more of the documents named above in the main and divisional applications.
The qualitative aspect of present objection depends on the invention which will chosen in the parent and divisional applications to come.

(ii) demethylating said intermediate compound of formula (III) obtained by step (i) so as to yield (±)duloxetine; and

(iii) converting (±)duloxetine obtained in step (ii) to (+)duloxetine by resolving racemic (±)duloxetine with di-p-toluyl tartaric acid so as to obtain (+)duloxetine di-p-toluyl tartrate, substantially free of (-)duloxetine, and converting said (+)duloxetine di-p-toluyl tartrate to (+)duloxetine hydrochloride.

12. A process according to any of claims 7 to 11, wherein the base is selected from the group consisting of an alkali metal hydroxide, an alkali metal carbonate and an alkali metal bicarbonate.

13. A process according to claim 12, wherein the base is selected from the group consisting of potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate and sodium bicarbonate.

14. A process according to any of claims 7 to 13, where the phase transfer catalyst is selected form the group consisting of crown ethers, quaternary ammonium salts and phosphonium salts.

15. A process according to claims 7 to 10, wherein X is hydroxy and Y is a leaving group.

16. A process according to claim 15, wherein the leaving group is halo.

17. A process according to claim 16, wherein the leaving group is fluoro.

18. A salt of a chiral acid and (+)duloxetine, containing not more than 1% of (-)duloxetine.

19. A salt of a chiral acid and (+)duloxetine, substantially free of (-)duloxetine, selected from the group consisting of (+)duloxetine mandelate, (+)duloxetine tartrate, (+)duloxetine di-p-toluyl tartrate, (+)duloxetine dibenzoyl tartrate and (+)duloxetine camphor sulfonate.